PROTEUS Trial: Neoadjuvant Apalutamide Plus ADT in High-Risk Prostate Cancer

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> For patients with high-risk localised prostate cancer, radical prostatectomy offers curative intent, yet a significant proportion experience biochemical recurrence. The clinical dilemma centres on optimising outcomes in this population, particularly those with adverse pathological features. The PROTEUS trial suggests that adding neoadjuvant apalutamide to androgen deprivation therapy (ADT) before surgery may improve pathological response, potentially altering the current surgical playbook.

KEY TAKEAWAYS

- The Pivot: Neoadjuvant apalutamide plus ADT improved pathologic complete response (pCR) and near-pCR rates compared to ADT alone.
- The Data: The pCR rate was 21.0% for apalutamide plus ADT versus 4.4% for ADT alone (p The Action: Clinicians should consider the potential benefits of intensified neoadjuvant therapy for high-risk prostate cancer patients undergoing radical prostatectomy, pending further long-term outcome data.

High-risk localised prostate cancer, defined by factors such as Gleason score 8-10, PSA >20 ng/mL, or clinical stage T3/T4, presents a challenge in management. Despite radical prostatectomy, a substantial number of patients experience disease recurrence, necessitating further treatment.1 Neoadjuvant androgen deprivation therapy (ADT) has been explored to downstage tumours and improve surgical outcomes, but its impact on long-term survival has been modest. The PROTEUS trial aimed to evaluate whether intensifying neoadjuvant therapy with apalutamide, a second-generation androgen receptor inhibitor, in combination with ADT, could improve pathological outcomes in this patient population.2 Prostate cancer is the second most common cancer in men globally, with an estimated 1.4 million new cases diagnosed in 2020. Approximately 15-20% of these cases are classified as high-risk localised disease. For these patients, standard treatment often involves radical prostatectomy or radiation therapy, frequently combined with ADT. However, biochemical recurrence rates can still be as high as 30-50% within five years, highlighting the need for more effective upfront strategies. Apalutamide, a potent androgen receptor inhibitor, works by binding directly to the androgen receptor, preventing androgen binding, androgen receptor nuclear translocation, and DNA binding, thereby inhibiting androgen receptor-mediated gene transcription and tumour cell proliferation. This mechanism of action offers a rationale for its use in combination with ADT to achieve more profound androgen deprivation and potentially better tumour control in the neoadjuvant setting.

Study Design and Findings

The PROTEUS trial was a phase 3, randomised, double-blind, placebo-controlled study. It enrolled 1,071 patients with high-risk or very high-risk localised prostate cancer who were candidates for radical prostatectomy. Patients were randomised 1:1 to receive either apalutamide 240 mg daily plus ADT or placebo plus ADT for 6 months prior to radical prostatectomy. The primary endpoint was pathologic complete response (pCR) and near-pCR, defined as 2
Patient eligibility criteria included histologically confirmed adenocarcinoma of the prostate, high-risk or very high-risk disease features (e.g., Gleason score 8, PSA >20 ng/mL, or clinical stage T3-T4), an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate organ function. Patients with prior systemic therapy for prostate cancer, prior orchiectomy, or metastatic disease were excluded. The study design ensured a balanced distribution of prognostic factors between the two treatment arms, enhancing the reliability of the comparative analysis. The ADT regimen typically involved a luteinizing hormone-releasing hormone (LHRH) agonist or antagonist, administered according to standard clinical practice. The 6-month neoadjuvant treatment duration was chosen based on prior studies indicating its potential for tumour downstaging without unduly delaying definitive surgery.
The trial demonstrated a statistically significant improvement in the primary endpoint. The pCR rate was 21.0% (95% CI, 17.6-24.7) in the apalutamide plus ADT arm compared to 4.4% (95% CI, 2.9-6.3) in the placebo plus ADT arm (P 35.4% for the apalutamide plus ADT group versus 14.7% for the placebo plus ADT group (P 3
Subgroup analyses consistently favoured the apalutamide plus ADT arm across various baseline characteristics, including Gleason score, clinical T-stage, and PSA levels. Adverse events were generally consistent with the known safety profiles of apalutamide and ADT. Grade 3 or 4 adverse events occurred in 30.2% of patients in the apalutamide plus ADT arm and 20.3% in the placebo plus ADT arm. The most common adverse events in the apalutamide arm included fatigue, rash, and hypertension, which were manageable and typically resolved with dose modification or supportive care.3

Limitations and Next Steps

While the PROTEUS trial demonstrated a significant improvement in pathological response rates, it is important to note that pCR and near-pCR are surrogate endpoints. Long-term follow-up is ongoing to determine if these pathological improvements translate into a meaningful benefit in event-free survival and overall survival. The median follow-up for EFS was 30.3 months, which is relatively short for prostate cancer outcomes.3 The increased incidence of Grade 3 or 4 adverse events in the intensified therapy arm also warrants careful consideration regarding patient selection and tolerability. Further research is needed to identify specific patient subgroups who would derive the greatest benefit from this intensified neoadjuvant approach, balancing efficacy with potential toxicity. The cost-effectiveness of adding apalutamide to neoadjuvant ADT also requires evaluation.
Another limitation involves the generalizability of the findings. The trial population consisted of patients eligible for radical prostatectomy, potentially excluding those with comorbidities or very locally advanced disease who might be candidates for other treatment modalities. The impact of this intensified neoadjuvant regimen on quality of life, beyond the reported adverse events, also requires further investigation. Future studies could explore biomarkers to predict response to apalutamide plus ADT, potentially allowing for more personalized treatment approaches. Additionally, comparisons with other intensified neoadjuvant regimens, such as those incorporating chemotherapy or radiation, could provide a broader understanding of optimal strategies for high-risk localised prostate cancer.

CLINICAL IMPLICATIONS

The PROTEUS trial's demonstration of improved pathological complete response rates with neoadjuvant apalutamide plus ADT is a compelling data point for high-risk localised prostate cancer. For urologists and radiation oncologists, this raises the immediate question of whether to incorporate intensified neoadjuvant therapy into current practice. While a 21% pCR rate is clinically meaningful, the absence of mature long-term survival data means that a wholesale shift in the standard of care is premature. Clinicians will need to weigh the benefits of improved pathological outcomes against the increased toxicity profile and the current lack of definitive event-free or overall survival advantage. This is not a simple addition to the treatment algorithm; it demands a nuanced discussion with patients regarding potential benefits and risks.

From a pharmaceutical industry perspective, this trial reinforces the value of second-generation androgen receptor inhibitors in earlier disease settings. Janssen, the developer of apalutamide, will undoubtedly leverage these results to advocate for expanded indications, potentially increasing market share in the neoadjuvant space. However, payers and guideline bodies, such as NCCN or EAU, will likely await more robust survival data before endorsing this as a new standard of care, particularly given the increased cost associated with adding apalutamide. The economic impact on healthcare systems, already strained, will be a significant consideration.

For patients, the prospect of a more effective neoadjuvant regimen is encouraging, offering hope for better disease control. However, they must be counselled on the trade-offs: a more intensive pre-surgical regimen with a higher likelihood of adverse events, without a guaranteed improvement in long-term survival at this stage. The decision to pursue this intensified therapy will require careful shared decision-making, ensuring patients understand the current evidence and the ongoing nature of the survival data collection. The dry precision of the trial data must be translated into clear, balanced information for those facing this complex diagnosis.

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